中華醫誌 Chin Med J 1985;36:191-6.

EFFECTS OF SAN-HUANG-HSIEH-HSIN-TANG ON BLOOD PRESSURE, SERUM LIPIDS AND LOCOMOTOR ACTIVITY IN RATS

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(Accepted 5 April 1985)

The formula of San-Huang-Hsieh-Hsin-Tang was originally described by Chang TC (張仲景) about 2000 years ago for patients who had "epigastric fullness, flushing up, restlessness, neckstiffness and constipation". All these symptoms are frequently observed in patients with essential hypertension. We studied the effects of San-Huang-Hsieh-Hsin-Tang on blood pressure, serum lipids and locomotor activity of male Sprague-Dawley rats.

Using different preparations of San-Huang-Hsieh-Hsin-Tang (S-H-T) (water-extracted, wine-prepared and alcohol-extracted), we found that the LD50 (95% confidence limit) of alcohol-extracted S-H-T, given by the intraperitoneal route, was 5.82 g/kg (5.58-6.05 g/kg) of original herb dosage. The alcohol-extracted S-H-T caused the most apparent dose-dependent hypotensive effect in anesthetized rats. The alcohol-extracted S-H-T also significantly lowered serum cholesterol and triglyceride, elevated serum HDL-c and depressed the locomotor activity of rats.

Keywords: herb and hypertension

The three components of San-Huang-Hsieh-Hsin-Tang (S-H-T) are 大黃 Rheum *officinale* BAILLON (*Polygonaceae*), 黃連 Coptis *chinensis* FRANCHET (*Ranunculaceae*), 黃芩 Scutellaria *baicalensis* GEORGE (*Labiatae*).[1] Berberine and Baicalin/Baicalein, the main constituents of Copits *chinensis* and Scutellaria *baicalensis* respectively, may have weak hypotensive effect.[2,3] Emodin in Rheum *officinale* may cause diarrhea.[4] Berberine, Baicalin and Baicalein may be alcohol-solubel. Emodin may be water-soluble. Chinese herb doctors use rice-wine to rinse the 3 components of S-H-T before they are boiled with water.[5] All the above facts raised us to think whether using different solvents to prepare S-H-T may affect the effectiveness and side effect (diarrhea) of S-H-T. Thus, different preparations (alcohol-extracted, wineprepared and water-extracted) of S-H-T were used to study its effects on LD50 and blood pressure in rats. Then we used the preparation with the most apparent hypotensive effect to study its effects on serum cholesterol, triglyceride and HDL-c and locomotor activity.

METHODS

Preparations of S-H-T

In this study, we used three different preparations of S-H-T: alcohol-extracted, water-extracted and wine-prepared.

The alcohol-extracted S-H-T was prepared by the following way: The mixture (1 kg) of powders of Rheum *officinale* BAILLON (*Polygonaceae*), Coptis *chinensis* FRANCHET (*Ranunculaceae*) and Scutellaria *baicalensis* GEORGE (*Labiatae*), in the ratio of 1:2:3, was immersed in 5000 ml of 95% alcohol at room temperature for 3 days. The extract was evaporated and concentrated in a rotary vacuum evaporator at a temperature just below 60°C. The concentrated extract was lyophilized and then pulverized through

a No. 80# mesh.

In the water-extracted S-H-T, the solvent used was pure water.

In the wine-prepared S-H-T, the 3 components of S-H-T were initially rinsed with rice-wine and then boiled with pure water.

When given to rats, the preparations were suspended in 0.5% carboxymethylcellulose (CMC) solution.

Acute toxicity

Male Sprague-Dawley rats weighting between 180 and 200 g were used. According to the method of Litchfield and Wilcoxon, the LD50s' (95% confidence limits) were assessed 24 hours after oral or intraperitoneal administration of each preparation.

Blood pressure

Male Sprague-Dawley rats weighting between 250 and 280g were anesthetized by urethane (1.0g/kg, I.P.). One carotid artery was cannulated by a polyethylene tube and then connected to a volumetric transducer. Both blood pressure and respiration were recorded by a polygraph (Nihon Kohden Multipurpose). After a steady state was obtained, three preparations of S-H-T were administered intraperitoneally respectively to assess the hypotensive effects.

Serum cholesterol, triglyceride and HDL-c

Eighteen rats weighting between 180 and 200g were used and divided into 3 groups (A, B and C): In the A group, the rats were given normal diet throughout the whole couse of the experiment for 8 weeks. In the B group, the rats were given high lipid diet containing 2% cholesterol and 0.5% cholic acid for the 8 weeks. In the C group, the high lipid diet described above was given for the 8 weeks and the alcohol-extracted S-H-T (3.6g/kg/d) was administered orally from the 4th week to the 8th week. Serum cholesterol, triglyceride and HDL-c were checked weekly for 8 weeks.

Locomotor activity

Alcohol-extracted S-H-T (3.6g/kg) was administered orally to male Sprague-Dawley rats (180-200g). The Locomotor activity was measured by an animal locomotor meter (MK-Animex). The animal locomotor meter was placed in a sound-proofed, temperature-controlled, poorly-illuminated room used solely for this experiment. After treatment with S-H-T, the rats was placed in the locomotor meter. The sensitivity and tuning of the instrument was then adjusted to 35uA to enable all kinds of locomotor activity to be jointly recorded. Activity was recorded at 60-min intervals for 3 hours, starting 5 min after inserting the animal into the test cage. Each rat was used only once and totally 6 rats were used for each treatment.[6]

Statistical analysis

Results were analysed statistically using Student's t test to compare intergroup differences.

RESULTS

Acute toxicity

As shown in Table 1, by the oral route, the LD50s' of the 3 preparations were all more than 36.2g/kg. The LD50 (95% confidence limit) of the water-extracted S-H-T by the intraperitoneal route was 15.2g/kg (13.0-17.0g/kg). The LD50 (95% confidence limit) of the wine-prepared S-H-T by the intraperitoneal route was 11.1g/kg (8.4-14.1g/kg). The LD50 (95% confidence limit) of the alcohol-extracted S-H-T by the intraperitoneal route was 5.8g/kg (5.6-6.1g/kg). The dosages were expressed in the original herb dosages.

Effects on blood pressure

As shown in Table 2, the water-extracted S-H-T (0.9g/kg, I.P.) did not lower blood pressure. The wine-extracted S-H-T (0.9g/kg, I.P.) significantly lowered blood pressure only at around 1 hour after administering S-H-T. The alcohol-extracted S-H-T (0.9g/kg, I.P.) significantly lowered blood pressure after 30 min and the effect lasted for more than 3 hours. Table 3 shows the dose-dependent hypotensive effect of alcohol-extracted S-H-T.

Effects on serum cholesterol, triglyceride and HDL-c

As shown in Figure 1, 2 and 3, the

Table 1. LD50 and 95% confidence limit of different preparations of S-H-T in rats.

Preparation of S-H-T	Route	LD50 (95% confidence limit)
water-extracted	P.O.	> 36.23 g/kg
wine-prepared	P.O.	> 36.23 g/kg
alcohol-extracted	P.O.	> 36.23 g/kg
water-extracted	I.P.	15.21 g/kg (13.40-17.02 g/kg)
wine-prepared	I.P.	11.07 g/kg (8.38-14.06 g/kg)
alcohol-extracted	I.P.	5.82 g/kg (5.58-6.05 g/kg)

The above dosages are those of crude herb materials

Table 2. Effects of "San-Huang-Hsieh-Hsin-tang" on blood pressure (B.P.) in rats

Treatment	Dose g/kg (I.P.)	No. of rats	Systolic B.P./Diastolic B.P. (mmHg, Mean ± S.E.) 0	30′	1hr	2hr	3hr	4hr	5hr	6hr
water-extracted	0.9	6	133±1	132±2	132±3	131±2	130±2	130±1	131±2	131±3
			85±2	83±1	82±1	79±2	83±1	83±1	83±1	84±2
wine-extracted	0.9	6	126±3	123±2	117±2**	118±3	117±3	116±3	115±3	118±3
			75±3	73±4	69±5	68±3	67±4	69±4	70±4	70±5
alcohol-extracted	0.9	6	128±3	121±4*	114±5**	111±4**	111±3**	120±3	121±2	120±3
			81±3	67±6*	65±5**	61±3**	63±3**	70±5	71±5	65±4

Significant differences from the pretreatment values at time zero were noted by: *: $P < 0.05$ and **: $P < 0.01$.

Table 3. Dose-dependent relationship of alcohol-extracted S-H-T on B.P. in rats

Dose g/kg (I.P.)	No. of rats	Systolic B.P./Diastolic B.P. (mmHg, Mean ± S.E.) 0	30′	1hr	2hr	3hr	4hr	5hr	6hr
0.45	6	126±4	127±4	125±4	126±4	126±4	126±5	125±4	123±4
		72±3	72±3	72±3	73±3	73±4	72±4	73±3	73±4
0.9	6	128±3	121±4*	114±5**	111±4**	111±3**	120±3	121±2	120±3
		81±3	67±6*	65±5**	61±3**	63±3**	70±5	71±5	65±4
1.8	6	130±2	118±3*	116±3**	118±3**	112±3**	106±5**	102±4**	97±5**
		75±2	68±2**	66±2**	67±2**	63±3**	61±3**	58±3**	55±3**

Significant differences from the pretreatment values at time zero were noted by: *: $P < 0.05$ and **: $P < 0.01$.

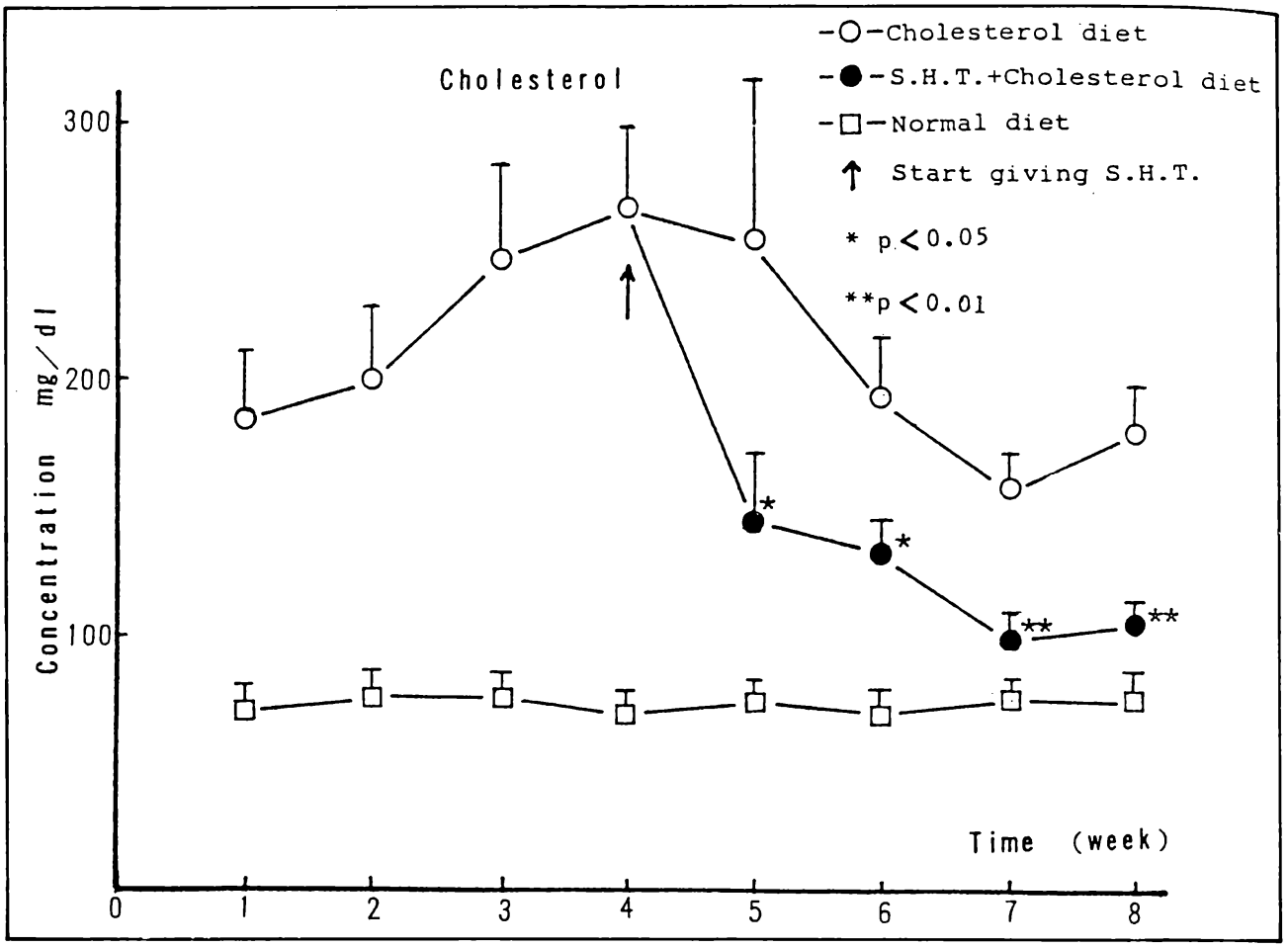

Figure 1. Effect of alcohol-extracted S-H-T on serum cholesterol in rats

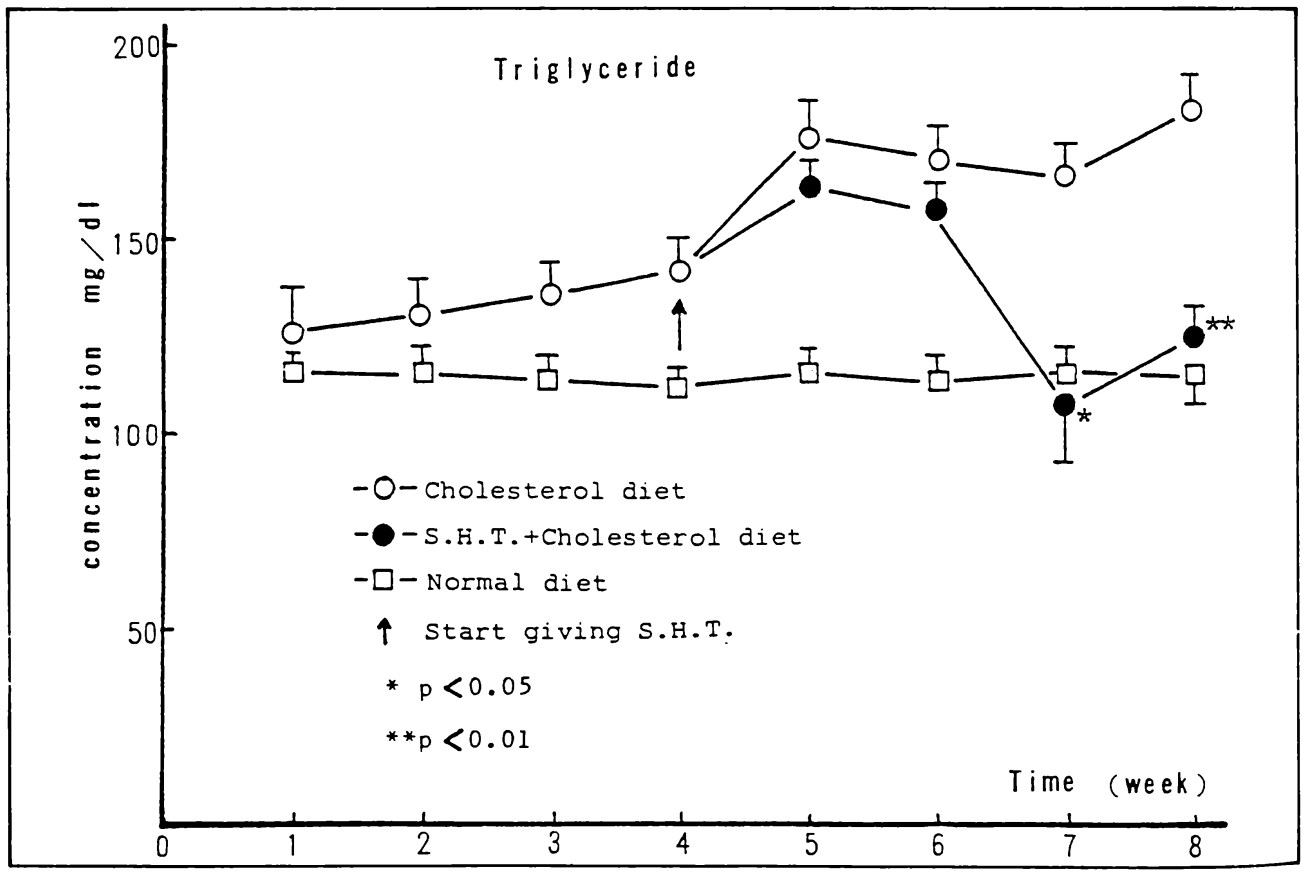

Figure 2. Effect of alcohol-extracted S-H-T on serum triglyceride in rats

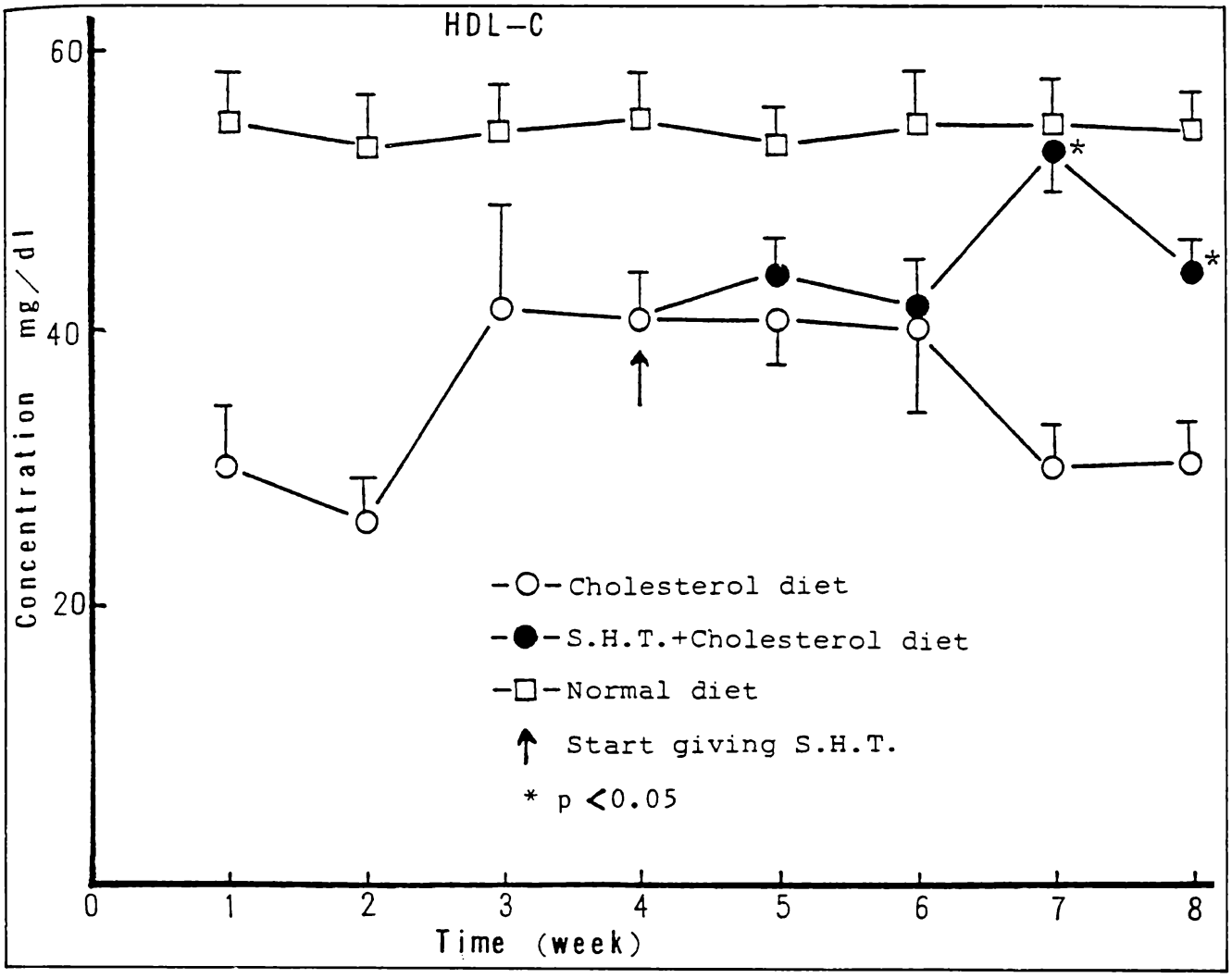

Figure 3. Effect of alcohol-extracted S-H-T on serum HDL-c in rats

serum cholesterol and triglyceride were significantly lowered and the serum HDL-c was significantly elevated by alcohol-extracted S-H-T.

Effect on locomotor activity

As shown in Figure 4, the locomotor activity was significantly lowered by alcohol-extracted S-H-T at dosages greater than 1.8g/kg, P.O. The higher the dosage, the greater the depressant effect.

DISCUSSION

In the three different preparations of S-H-T, we found that the alcohol-extracted S-H-T had the most apparent hypotensive effect. This may imply that the hypotensive component of S-H-T is alcohol-soluble.

The locomotor activity of rats was significantly dose-dependently depressed by the alcohol-extracted S-H-T. This may imply that

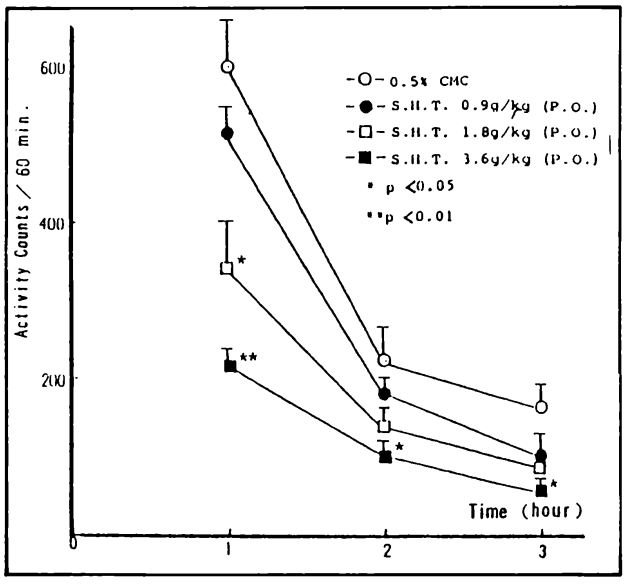

Figure 4. Effect of alcohol-extracted S-H-T on locomotor activity in rats

the S-H-T has its effect on the central nervous system. In an unpublished preliminary observation, by using patients with essential hy-

pertension or insomnia, the antihypertention, antianxiety and antiinsomnia effects of alcohol-extracted S-H-T were also confirmed by detecting its effects on orthostatic changes in heart rate and blood pressure,[7] on the Hamilton anxiety scale,[8] on the EEG pattern. All these results imply that the alcohol-extracted S-H-T may act on the central nervous system with subsequent decrease in sympathetic outflow.

In this study, we also confirmed that the alcohol-extracted S-H-T significantly lowered serum cholesterol and triglyceride and elevated serum HDL-c. This has been reported by Aonum et al.[9] This implies that the alcohol-extacted S-H-T has some protective effect on the cardiovascular system in the aspect of preventing atherosclerosis. The lowering in serum cholesterol is significantly greater than the lowering in serum triglyceride. This may imply that the S-H-T blocks the biochemical pathway between triglyceride and cholesterol.

Our further works are to study the changes of monoamines in the central nervous system and the peripheral blood. These may lead us to further understand the mechanism of S-H-T.

ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to Kuo, Jung-Chao, Dr. Chow, Hsue-Chung and Professor Chen Chien-Fu for their invaluable help. This work is supported by the National Science Council, R.O.C. (Grant NSC 73-0412-B039-03).

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三黃瀉心湯對大白鼠血壓、血脂肪與自發運動量之影響

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我們研究以不同之方法製備之三黃瀉心湯（水抽取，酒炮製與酒精抽取）對降壓作用之影響：發現用酒精抽取之三黃瀉心湯具有最明顯之降壓效果。其降壓效果因劑量之增加而增加。

我們發現酒精抽取之三黃瀉心湯具有降低血中膽固醇，三酸甘油脂及增加血中高密度脂蛋白之作用，亦具有抑制大白鼠自發運動量之作用。三黃瀉心湯之降壓效果可能與交感神經的活性被抑制有關。

（Chin Med J 1985;36:191-6.）